PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Rothermel and Williams

Serial No.: ~~09/061,417~~

Filed: February 13, 2001

For: METHODS AND COMPOSITIONS RELATING TO MUSCLE SELECTIVE CALCINEURIN INTERACTING PROTEIN (MCIP)

Group Art Unit: 1653

Examiner Samuel W. Liu

Atty. Dkt. No.: MYOG:036US/HYL

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

July 1, 2003
Date

Steven L. Highlander

DECLARATION OF ERIK BUSH UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Erik Bush, do declare the following:

1. I currently hold the position of Scientist at Myogen, Inc., licensee of the above-captioned application. My education and training includes an undergraduate degree in Biological Sciences from the University of Wisconsin and a Ph.D. in Cellular and Developmental Biology from the University of Colorado Health Sciences Center. In addition to my formal scientific training, I have over ten years of specialized training in the biology of human heart failure. Since 1992, I have been continuously involved in the study of

cardiovascular signal transduction and the regulation of gene expression in the normal, hypertrophied and failing myocardium. For the past three and a half years, I have been exclusively engaged in the discovery and validation of molecular drug targets for use in drug discovery in the field of heart failure. Currently, I am leading a research effort to discover small molecules capable of increasing expression of endogenous MCIP1 protein in cardiomyocytes. A copy of my *curriculum vitae* is attached.

2. I am also familiar with the level of skill of scientists working in the field of cardiology and molecular biology as of the priority date of the referenced application. I consider one of ordinary skill in the art in this field of study to have a Ph.D. in biochemistry, chemistry, molecular biology, pathology or other related field, or an M.D., with 1-3 years of post-graduate study.

3. I have reviewed the specification and pending claims 59-62 and claim 70 for the above-referenced case. The application claims a method for modulating muscle cell growth by providing for a modulator of MCIP (as amended the claims will refer only to MCIP1) and administering that modulator to cells to cause a modulation of muscle cell growth. There is an additional limitation to mammalian cells. Moreover, the claims have been limited to agonists and specifically peptide and small molecule agonists of muscle cell growth. Lastly, there is a claim to a method of administering to a mammal a pharmaceutical agent to treat cardiac disease.

4. The inventors' paradigm, as set out in the above-captioned application, suggests a method for tissue-selective inhibition of the calcineurin pathway in the heart. Signaling via the phosphatase calcineurin has a well-defined role in the development of maladaptive

cardiac hypertrophy. However, the development of small molecule inhibitors of calcineurin (such as cyclosporine) to attenuate cardiac hypertrophy has been limited by two factors: 1) the broad tissue distribution of this key phosphatase; and 2) the relative abundance of cardiac calcineurin (the heart expresses approximately ten times more calcineurin than other tissues).

5. The therapeutic use of calcineurin inhibitors to attenuate maladaptive cardiac hypertrophy will therefore likely require the development of tissue-selective calcineurin inhibitors. The discovery of endogenous calcineurin inhibitory proteins (MCIPs), whose expression is primarily restricted to striated muscle, has suggested just such a mechanism for the selective inhibition of calcineurin in the heart. Expression of inhibitory MCIP protein is increased in the heart in response to elevated calcineurin activity, thus providing a feedback mechanism to keep cardiac calcineurin activity in check. To this end, the inventors hypothesized that augmenting expression of endogenous MCIP protein may provide a tissue-selective method for the inhibition of calcineurin activity and maladaptive cardiac hypertrophy.

6. I have reviewed the enclosed article by Hill *et al.*, entitled "Targeted Inhibition of Calcineurin in Pressure-Overload Cardiac Hypertrophy: Preservation of Systolic Function," which supports the inventors' claims relating to MCIP as a therapeutic target. The Hill *et al.* authors set out to examine whether over-expression of MCIP1 protein inhibited the heart's hypertrophic response to a pathologically relevant hypertrophic stimulus: pressure overload. In the study, wild-type and MCIP1 over-expressing transgenic mice were subjected to thoracic aortic banding, a surgical procedure that induces pressure overload. Wild-type mice developed left ventricular hypertrophy, with

a 70% increase in heart mass normalized to body mass. The MCIP1 over-expressing transgenic mice exhibited a significant reduction in cardiac hypertrophy, with only a 40% increase in heart mass normalized to body mass. Furthermore, echocardiographic measurements confirmed that systolic function was well preserved in MCIP1 transgenic animals, even after three months of pressure overload. The authors conclude that "these data suggest that MCIP1 may be an endogenous regulator of hypertrophic signaling in the heart that does not prevent normal heart growth and development", and that "MCIP1 up-regulation may be an attractive target for therapeutic intervention in patients with heart disease." I agree with their conclusions, as I believe the data convincingly demonstrate that increased expression of MCIP1 protein confers a significant cardioprotective effect through the attenuation of pathologic cardiac hypertrophy.

7. I understand the examiner to be rejecting the claims in the current application because he alleges that the patent fails to describe any specific modulators of muscle cell growth or how to deliver them. I have reviewed the entire specification to address this issue. I find that the instant specification provides ample guidance for one of skill in the art to screen for, discover, and apply any of a variety of agonists that would both modulate muscle cell growth and/or MCIP1. The application further adequately describes how one would deliver these small molecules or pharmaceutical compositions to a cell, an animal, or a human patient. While the specification does not specifically list agents that would act as modulators, the guidance found in the specification is explicit, and it mirrors what can be seen throughout the literature of the art, that small molecules are considered advantageous in their use to modulate MCIP1 and that these small molecules are easily available to one of skill in the art. Furthermore, by following the very guidance in this

specification, my own work has succeeded in discovering small molecule agonists (*see infra*) that do indeed modulate muscle cell growth and modulate MCIP1 levels in muscle cells.

8. During the last two years, I have personally led a drug discovery effort to discover small molecules capable of increasing expression of endogenous MCIP1 protein in the heart. This research has been guided (as stated in paragraph 6 above) by the disclosures in the patent application, and the success of our efforts further validates the language of the application. In the course of our research, we identified a small molecule (compound #15) that significantly increased expression of endogenous MCIP1 protein in cultured rat neonatal ventricular myocytes (FIG. A; attached). This compound was also found to attenuate phenylephrine-dependent increases in total cellular protein and atrial natriuretic factor secretion, two *in vitro* markers of cardiac hypertrophy (FIGS. B and C; attached). Furthermore, this compound also normalized the maladaptive changes in myosin heavy chain expression associated with cardiac hypertrophy. As part of the fetal gene program induced during cardiac hypertrophy, expression of α myosin heavy chain protein decreases while expression of β myosin heavy chain increases. We observed that exposure to compound #15 significantly increased alpha myosin heavy chain protein and decreased beta myosin heavy chain protein in cardiac myocytes (FIG. D; attached). Our results are consistent with the inventors' paradigm that increased MCIP expression would inhibit cardiac hypertrophy. We are currently in the process of validating whether the anti-hypertrophic properties of compound #15 are a direct result of increased MCIP1 expression.

9. We also identified a different small molecule (compound #18) that similarly increased expression of endogenous MCIP1 protein in cultured rat neonatal ventricular myocytes. Compound #18 induced a different isoform of MCIP1 than compound #15, however, and had a different effect on cardiomyocyte growth. Compound #18 strongly promoted cardiomyocyte growth, inducing significant increases in cell volume, total protein, and expression of ANF and beta myosin heavy chain.

10. In conclusion, the authors of the Hill *et al.* article demonstrate that increased expression of MCIP1 protein is sufficient to significantly attenuate pressure-overload cardiac hypertrophy *in vivo*. Furthermore, our observations that a small molecule capable of increasing MCIP1 protein also attenuates cardiac hypertrophy *in vitro* supports the inventors' paradigm that strategies to augment MCIP1 expression may provide therapeutic benefit to individuals suffering from hypertrophic cardiomyopathy. Lastly, the application gives one of skill in the art more than sufficient guidance to gain possession of modulators of MCIP1 as well as sufficient description as to how to apply and use those modulators, and it is clear to me that the inventors had possession of this invention at the time they submitted the application. Our own recent data supports and validates the inventors model, their assertions, and my conclusions regarding the specification.

11. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

6/19/03
Date

Erik Bush, Ph.D.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Rothermel and Williams

Serial No.: ~~09/061,417~~

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For: METHODS AND COMPOSITIONS RELATING TO MUSCLE SELECTIVE CALCINEURIN INTERACTING PROTEIN (MCIP)

Group Art Unit: 1653

Examiner Samuel W. Liu

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July 1, 2003
Date

Steven L. Highlander

DECLARATION OF BEVERLY ROTHERMEL AND R. SANDERS WILLIAMS

UNDER 37 C.F.R. §1.131

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Beverly Williams and R. Sanders Williams, do declare the following:

1. We are citizens of the United States. Beverly Rothermel resides at 1409 Schumac Lane, Bedford, TX 76022 and R. Sanders Williams resides at 2 Pilling Place, Durham, NC 27707.

2. R. Sanders Williams currently holds the position of Dean of the Medical School at Duke University. Beverly Rothermel currently holds the position of Assistant Professor at The University of Texas Southwestern Medical Center at Dallas.

3. R. Sanders Williams is the first inventor listed as an inventor in the above-captioned application and Beverly Rothermel is the second inventor listed as an inventor for the same.

4. "Methods and Compositions Relating to Muscle Selective Calcineurin Interacting Protein (MCIP)" was conceived followed by diligence prior to the cited reference Fuentes *et al.*, July 1, 2000. As support of this statement, we have attached to this Declaration the intellectual property questionnaire for this invention. This questionnaire shows conception and possession of the invention prior to the cited reference, which was followed subsequently with diligent research up to the time of filing.

5. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date

Beverly Rothermel

6/27/03

Date

R. Sanders Williams

5. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

6/11/03
Date

Beverly Rothermel

Date

R. Sanders Williams

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Rothermel and Williams

Serial No.: ~~09/961,417~~

Filed: February 13, 2001

For: METHODS AND COMPOSITIONS RELATING TO MUSCLE SELECTIVE CALCINEURIN INTERACTING PROTEIN (MCIP)

Group Art Unit: 1653

Examiner Samuel W. Liu

Atty. Dkt. No.: MYOG:036US/HYL

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Steven L. Highlander

DECLARATION OF BEVERLY ROTHERMEL AND R. SANDERS WILLIAMS

UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Beverly Williams and R. Sanders Williams, do declare the following:

1. We are citizens of the United States. Beverly Rothermel resides at 1409 Schumac Lane, Bedford, TX 76022 and R. Sanders Williams resides at 2 Pilling Place, Durham, NC 27707.

2. R. Sanders Williams currently holds the position of Dean of the Medical School at Duke University. Beverly Rothermel currently holds the position of Assistant Professor at The University of Texas Southwestern Medical Center at Dallas.

3. R. Sanders Williams is the first inventor listed as an inventor in the above-captioned application and Beverly Rothermel is the second inventor listed as an inventor for the same.

4. Beverly Rothermel is the first author listed as an author and R. Sanders Williams is the sixth author listed as an author on "A protein encoded within the Down syndrome critical region is enriched in striated muscles and inhibits calcineurin signaling," J. Biol. Chem., 275:8719-8725, 2000.

5. Rick Vega, John Yang, Hai Wu, and Rhonda Bassel-Duby are listed as authors of the Rothermel *et al.*, paper, but are not inventors on the instant application.

6. The contribution of these individuals to the research discussed in the Rothermel *et al.*, paper is as follows: Rick Vega was a postdoctoral fellow who joined the Williams lab in August of 1999, a year after the MCIP/DSCR1 project was initiated and just prior to the beginning of our intellectual property discussions with our Office for Technology Development. Dr. Vega solely carried out the analysis of the physical interaction of MCIP with calcineurin presented in the paper. John Yang was a postdoctoral fellow who performed the northern blot analysis of MCIP expression. Hai Wu was a graduate student in the lab who carried out some gene reporter assays. Rhonda Bassel-Duby contributed to the writing of the manuscript and provided consultation.

7. Thus, the non-inventor co-authors of the Rothermel *et al.* paper did not make a conceptual contribution to the subject matter of that paper, and now claimed herein.

8. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date

Beverly Rothermel

6/22/03

Date

R. Sanders Williams

7. Thus, the non-inventor co-authors of the Rothermel *et al.* paper did not make a conceptual contribution to the subject matter of that paper, and now claimed herein.

8. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

6/11/03
Date

Beverly Rothermel

Date

R. Sanders Williams